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OTHER SOURCE(S): MARPAT 118:813

AB Biol. active mols. are disclosed which bind to and inhibit thrombin. These mols. comprise a catalytic site-directed moiety XR2(R1)R3R4R5R6Y (X = H, backbone chain of 1-100 atoms; R1 = unsubstituted or mono- or di- or trisubstituted saturated ring; R2 = bond, 1-5 atom backbone chain; R3 = bond, 1-3 atom backbone chain; R4 = amino acid; R5 = L-amino acid which comprises guanidinium- or amino-containing side chain; R6 = nonamide bond; Y = 1-9 atom backbone chain) or XR2(R1')R3R4'R5R6Y (R1' = unsubstituted or mono- or di- or trisubstituted ring; R4' = amino acid comprising a side chain with a capacity to accept an H bond at pH 5.5-9.5; X, R2, R3, R5, R6, Y as above). Preferred thrombin inhibitors are characterized by an anion binding exosite associating domain (ABEAM) and a linker portion of 18-42Å in length which connects Y to the ABEAM. Also disclosed are compns., combinations, and methods which employ these mols. for therapeutic, prophylactic, and diagnostic purposes. Hirulog-8 [H-(D-Phe)-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu-OH] (I) was synthesized with standard solid-phase synthesis methodol. The X-ray crystallog. structure of the I-thrombin complex was obtained and used to design I analogs. In addition to showing enhanced antithrombin activity in vitro over I, D-cyclohexylalanyl-I also

showed a significantly increased anticoagulant effect in plasma assays over I.